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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/575,061	05/19/2000	STEPHAN R. TARGAN	P-PM 4097	1578

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 09/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/575,061	TARGAN ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 14-22* is/are pending in the application.

4a) Of the above claim(s) *22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-7 and 14-22* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/8/05 has been entered.

Amendment Entry

2. Applicant's amendment and response filed 3/8/05 is acknowledged and has been entered. Claims 8-13 have been cancelled. Claims 14-22 have been added. Claims 1-7 and 14-22 are pending.

Election/Restrictions

3. A restriction requirement has been set forth in light of the newly submitted claims in addition to the claims currently pending of record, which are deemed to encompass two groups of inventions.

Restriction to one of the following inventions is required under 35 U.S.C. 121 :

I. Claims 1-7 and 14-21, drawn to method of diagnosing Crohn's disease using IgA OmpC antibodies as markers, classified in class 435, subclass 7.21

II. Claim 22, drawn to a method of diagnosing Crohn's disease in a subject using IgA OmpC antibodies, IgA ASCA antibodies, IgA anti-I2 polypeptide antibodies, and pANCA antibodies classified in class 436, subclass 811.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability, and (2) that the subcombination has utility by itself or in other combinations (MPEP § 806.05(c)). In the instant case, the combination as claimed does not require the particulars of the subcombination as claimed because the subcombination utilizes the specificity of a single marker to show a diagnosis of Crohn's disease. The subcombination has separate utility such as for use in affinity chromatography to isolate and purify specific antibodies from a sample. Accordingly, newly submitted claim 22 of Invention II is directed to an invention that is independent or distinct from the invention originally claimed.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 22 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 1-7 and 14-22 are pending. Claims 1-7 and 14-21 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 15, 16, and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is vague and indefinite in reciting, "[microbial antigens] other than OmpC associated with Crohn's" because the phrase "other than" includes elements not actually disclosed (those encompassed by "other than OmpC"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d). Additionally, the term "associated" is a subjective term that lacks a comparative basis for defining its metes and bounds. It is specifically unclear how one or more antigens and the presence or absence thereof, is *associated* to Crohn's disease.

Claim 16 is vague and indefinite in reciting, "associated" because the term "associated" is a subjective term that lacks a comparative basis for defining its metes and bounds. It is specifically unclear how one or more antigens and the presence or absence thereof, is *associated* to Crohn's disease.

In claim 18 step b), line 2, "an" should be deleted before "one or more".

In claim 18, step c), line 1 after "contacting said complexes", --with-- should be inserted.

Claim 18 is vague and indefinite because it is unclear how the presence or absence of IgA OmpC and the presence or absence of ASCA in step d) can be differentially detected using labeled anti-IgA antibody that does not appear to have

differential specificity between IgA anti-OmpC and ASCA. Moreover, it is unclear how the presence of IgA anti-OmpC and the presence of ASCA each can independently and differentially provide an indication of a subject having Crohn's disease using labeled anti-IgA antibody that does not appear to be specific for either one of IgA anti-OmpC and ASCA. Same analogous comments and problems apply to claim 19.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 and 14-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for all of IgA outer membrane protein C (OmpC) antibody, anti-Saccharomyces antibody (ASCA), I-2 polypeptide antibody (I-2 antibody), and perinuclear anti-neutrophil antibodies (pANCA) as cumulative diagnostic markers for use in a method for diagnosing the presence of Crohn's disease, does not reasonably provide enablement for using only solely IgA anti-OmpC antibody as a diagnostic marker for diagnosing the presence of Crohn's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQZd 1400 (Fed. Cir. 1988), enablement requires that the specification teach those skilled in the ad to make and use the invention without undue experimentation. Factors to be considered in determining,

whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method of diagnosing CD in a subject by determining the presence of IgA OmpC antibody in the subject using OmpC antigen, ASCA, I-2 polypeptide antibody, and PANCA, wherein the presence of all of IgA OmpC, ASCA, I-2 antibody, and PANCA antibody in a diagnostic system, is diagnostic of the presence of CD in the subject.

The state of the prior art- the prior art of record fails to disclose a method of diagnosing CD in a subject by determining the presence of IgA OmpC antibody in the subject using OmpC antigen, wherein the presence of IgA OmpC antibody is diagnostic of the presence of CD in the subject.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed method will work for diagnosing the presence of CD using IgA OmpC antibody using OmpC antigenic reactive fragments, alone, and without combination with ASCA, I-2 antibody, and PANCA in a diagnostic system.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to work using a diagnostic system comprising IgA OmpC antibody detected using OmpC antigen, ASCA, I-2 antibody, and PANCA in diagnosing the presence of CD in a subject.

The presence or absence of working examples- working examples are provided in the specification that show diagnosis of CD using a diagnostic system comprising IgA OmpC detected using OmpC antigen, ASCA, I-2 antibody, and pANCA for diagnosing the presence of CD in a subject. There are no working examples that show analogous diagnostic results using each one of IgA OmpC detected using OmpC antigen, ASCA, I-2 antibody, and pANCA, individually and independently, for diagnosing the presence of CD. The quantity of experimentation necessary it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art - the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method of diagnosing CD in a subject by determining the presence of IgA OmpC antibody using OmpC antigen or a reactive fragment thereof, wherein the presence of IgA OmpC or ASCA or I-2 antibody, is individually and independently, diagnostic of the presence of CD in the subject.

With regards to diagnosis of Crohn's disease, while the specification provides that detection of IgA OmpC antibody in a subject using OmpC antigen in the claimed assay method (page 3) is contributory to the diagnosis of CD, the specification does not show any working examples that suggest or support the claimed method using only IgA OmpC antibody as a sole diagnostic marker of CD. Page 6, Table 1, and Figures 1 and 2 of the specification discloses that IgA OmpC antibody in addition or combination to ASCA, I-2 polypeptide antibody, and pANCA provides a highly sensitive diagnostic system which can detect 86% of patients with CD, but provides no showing that the

claimed method works in using only IgA OmpC antibody. Table 2 shows that IgA OmpC reactivity detected only 55% of patients having CD while ASCA, I-2 polypeptide antibody, and pANCA show detection capability of 56%, 52%, and 24% only, respectively, individually and independently. Additionally, the fact that the claimed method appears to work in identifying 55% of patients having CD is not sufficient to enable the breadth of the claimed method for using IgA OmpC as a sole diagnostic marker of CD in patients.

State of the art literature by Joosens et al. provide use of IgA OmpC antibody, ASCA, I-2 polypeptide, and pANCA as a panel to investigate its capacity to diagnose CD in subjects having IBD. Joosens et al. determined, based on their study, that the predictive value towards differentiation of CD in IBD patients is 75% in comparison to ASCA / pANCA panel which is 66.7% and concluded that adding IgA OmpC antibody and I-2 polypeptide as new markers in combination with ASCA and pANCA, increases predictive value towards diagnosis of CD. Joosens et al. stated that IgA OmpC antibodies are specific for CD, but only found the marker in 30-35% of patients having IBD (specificity).

State of the art literature by Zhouludev et al. also provide an evaluation of the sensitivity and specificity of a panel comprising pANCA, IgA ASCA, IgG ASCA, and IgA OmpC antibody. Zhouludev et al. determined that ASCA antibodies were identified in 44% of CD patients, pANCA were found in 18% of CD patients, and IgA OmpC antibodies were found in 24% of CD patients and displayed a 5% false positive rate. Zhouludev et al. stated that IgA OmpC antibody identified a small number of IBD

patients not detected by other markers. Zhouludev et al. concluded based on the statistics that anti-OmpC antibody as an isolated assay, has low sensitivity for diagnosis of CD. Alternatively, Zouludev et al. stated that a positive result of any of the four antibodies as serological markers would increase the overall sensitivity of the panel to 65% and specificity of the panel to 94% in the diagnosis of CD.

Accordingly, it appears that a cumulative effect between a group of markers such as the diagnostic system disclosed comprising IgA OmpC antibody, ASCA, 1-2 polypeptide antibody, and pANCA, is necessary in order to provide accurate determination of CD in a subject. While it is not necessary to show working examples for every possible embodiment disclosed in Applicant's specification, there should be sufficient teachings in the specification or predictability based on the state of the art, that would suggest to the skilled artisan that the breadth of the claimed method is supported and enabled. This is not the case in the instant disclosure. Thus, the claimed method is only enabled for a diagnostic system comprising IgA OmpC antibody, ASCA, 1-2 polypeptide antibody, and PANCA as combined diagnostic markers in diagnosing the presence of CD.

In view of the teachings of In re Wands, 8 USPQZd 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed method for diagnosing CD using only IgA OmpC antibody as a diagnostic marker, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work in greater than 56% of CD patients, 3) there is no proper

guidance that shows that IgA OmpC antibody is an acceptable sole diagnostic marker for diagnosing the presence of CD, 4) the nature of the invention is a method of diagnosing CD in a subject by determining the presence of IgA OmpC antibody in the subject using OmpC antigen, ASCA, 1-2 antibody, and PANCA, wherein the presence of all of IgA OmpC, ASCA, 1-2 antibody, and PANCA antibody in a diagnostic system, is effective in diagnosing the presence of CD in a subject, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows that the claimed method will work for diagnosing the presence of CD in all patients using IgA OmpC antibody, alone, and without combination with ASCA, 1-2 antibody, and PANCA in a diagnostic system, and lastly 7) the claims broadly recite a method of diagnosing CD in a subject by determining the presence of IgA OmpC antibody using OmpC antigen or a reactive fragment thereof, wherein the presence of IgA OmpC or ASCA or 1-2 antibody, or pANCA is individually and independently, diagnostic of the presence of CD in the subject. Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Response to Arguments

6. Applicant's arguments filed 3/8/05 have been fully considered but they are not persuasive.

A) Applicant contends that FDA recognizes ASCA as a marker that aids in the diagnosis of Crohn's disease and do not disclose or suggest that in order for detecting

the presence or absence of ASCA to be useful in the diagnosis of CD, the detection of further IgA antibodies for additional microbial antigens is necessary. According to Applicant, since the percentage of Crohn's disease having ASCA is comparable to those having IgA OmpC antibodies, then it follows that detecting the presence or absence of IgA OmpC antibodies would also be recognized by FDA as a useful aid in the diagnosis of Crohn's disease.

In response, Applicant's argument that FDA's recognition of ASCA as a marker aids in diagnosing Crohn's disease has low probative value and does not have any bearing in as far as supporting Applicant's claim of IgA OmpC antibody as being a sole and isolated marker for diagnosing CD because FDA has not shown that ASCA can statistically be a sole and isolated marker for CD and only provided that it can aid in diagnosing CD. Similarly, IgA OmpC antibody can also aid as a marker in diagnosing CD. However, the statement of "aid to diagnosis of CD" does not exclude the need for other serological markers to provide a cumulative effect of providing diagnostically acceptable levels of accuracy, sensitivity, and predictability in achieving actual determination of CD in a given subject, as opposed to ulcerative colitis, indeterminate colis, or any other irritable bowel disease.

B) Applicant argues that detection of the presence or absence of IgA anti-OmpC antibodies provides an independent diagnostic marker for CD by virtue of the specificity of the method. According to Applicant, in about 28 individuals without CD, only 1 tested

for positive IgA OmpC antibodies, which accounts for its high specificity as an independent marker for CD.

In response, Applicant's data in the specification has not provided that presence of IgA anti-OmpC antibody defines a nexus with the diagnosis of CD, absent further confirmation by any other detection marker of CD. Joosens et al. stated that IgA OmpC antibodies are specific for CD; however, it is only found in 30-35% of CD patients. Zhouludev et al. stated that IgA OmpC antibodies specified a small number of IBD patients not detected by other markers, but failed to remark on its specificity for CD. A patient population of 28 subjects could not have taken into account any other population that may potentially carry IgA OmpC antibodies, but not symptomatic of IBD. The Office is not a testing laboratory and is thus, not equipped to obtain actual evidentiary showing defining that such a nexus indeed exists between the presence of IgA anti-OmpC antibody and the indication diagnostic of Crohn's disease in a general population. Absent evidentiary showing that a correlation exists between the presence of IgA anti-OmpC antibody and actual diagnosis of Crohn's disease in 55% of any given population, the specification is not enabled for the recited claimed invention.

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571)

272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
April 15, 2005

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04/18/05